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Non-Surgical Options for The Diagnosis of Endometriosis in Low-Resource Settings: A Comparative Study

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Purpose: Endometriosis, a chronic estrogen-dependent condition characterized by the implantation of tissue beyond the uterine cavity, impacts 10% of women of reproductive age. Endometriosis manifests through menstrual discomfort, chronic pelvic pain, dyspareunia, and cyclical digestive issues. It is additionally linked to infertility. Early diagnosis and effective treatment are crucial but remain limited in many settings. This study aims to identify specific clinical characteristics that could aid in the early diagnosis and treatment of endometriosis.

Patients and Methods: The study conducted at Province General Hospital Margono, Indonesia, involved endometriosis patients who had registered from 2020 to 2024. Some inclusion and exclusion criteria are applied in this study. Statistical analysis was performed to determine the rate, odd ratio and prevalence ratio.

Results: Our analysis indicates that women experiencing dysmenorrhea, particularly with an onset occurring more than three years after menarche, are significantly associated with endometriosis. Dysmenorrhea had nearly 17.5 times higher odds [OR 17.5, 95% CI 4.75–64.4, p-value 0.00] of being correlated with endometriosis, and the onset of dysmenorrhea more than 3 years after menarche had 1.67 times higher [OR 2.790; CI 95%; 1.011–7.698, p-value 0.045] of being associated with endometriosis.

Conclusion: Multiple studies have shown that diagnosing endometriosis early is challenging due to its various symptoms. Our findings highlight the significance of dysmenorrhea characteristics, particularly its onset timing, as potential indicators of endometriosis. This findings suggest that incorporating dysmenorrhea onset into clinical assessments may enhance non-surgical diagnostic approaches, facilitating earlier detection and management of endometriosis.

Keywords: predictive model, menstrual cycle, endometriosis, non-invasive

Introduction

Endometriosis is one of the primary reproductive problems. Endometriosis is a chronic estrogen-dependent condition marked by the ectopic implantation of functioning uterine lining tissue (endometrial glands and stroma) outside the uterine cavity.[1] Endometriosis impacts around 10% (190 million) of women and girls of reproductive age worldwide.[2] Endometriosis is estimated to impact roughly 10% to 15% of women of reproductive age, with prevalence rising to as much as 70% in those with chronic pelvic pain.[3] However, prevalence estimates vary depending on the diagnostic method, ranging from higher rates in laparoscopically confirmed cases to lower rates in self-reported data. The prevalence of endometriosis varies from 0.7% to 45% in asymptomatic women, 20% to 40% in infertile women, 6% to 18% in women undergoing sterilization, and 15% to 70% in individuals with chronic abdominal pain.[4]

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Endometriosis is a complex and multifaceted condition influenced by a combination of genetic, hormonal, environmental, and immune system factors. Research has shown that these elements play a significant role in the development and progression of the disease.[5] Etiopathogenesis of this disease has been extensively investigated and explained in various theories, from clinical to biomolecular.[6] Based on Sampson's implantation theory, peritoneal endometriosis lesions develop from endometrial tissue, which flows retrograde through the fallopian tubes during menstruation.[7] This is also the most significant risk factor and cellular mechanism underlying pelvic endometriosis.[8] Immunity was also a significant factor in endometriosis development. Normally, the immune system recognizes and eradicates these aberrant cells; but, in endometriosis, this process is compromised. Essential immunological components involved are macrophages, which are present in elevated quantities and secrete growth factors and cytokines that facilitate the survival and proliferation of ectopic endometrial cells. Natural killer (NK) cells exhibit diminished activity in patients with endometriosis, resulting in a compromised capacity to identify and eliminate these aberrant cells.[9] Moreover, pro-inflammatory cytokines and chemokines are increased in the peritoneal fluid, creating an inflammatory milieu that facilitates the formation of endometrial lesions. T cells demonstrate modified responses, resulting in insufficient immune surveillance and the persistence of endometrial cells beyond the uterus. These immunological modifications exacerbate the persistent inflammation inherent to endometriosis, hence facilitating lesion formation and related symptoms.[10]

Signs and symptoms of endometriosis such as menstrual pain (62%), chronic pelvic pain (57%), dyspareunia (55%), cyclic intestinal complaints (48%) and infertility (40%).[11] Menstrual pain (dysmenorrhea) is the most frequently reported pain related to endometriosis. Menstrual pain related to endometriosis often begins before menstruation starts and persists throughout menstruation or even longer. This pain originates from within the pelvis, spreads, and can sometimes radiate to the back and thighs, causing other symptoms such as diarrhea. Chronic pelvic pain is severe pain in the pelvic area lasting more than 6 months, which can incapacitate patients and require treatment. Deep dyspareunia associated with endometriosis typically occurs before menstruation and becomes more painful at the start of menstruation. The most commonly reported cyclic intestinal complaints by patients include bloating (96%), diarrhea (27%), and constipation (16%). Endometriosis-related infertility can be caused by problems with the adnexa, which anatomically block or hinder ovum capture during ovulation, impact on oocyte development and reduced endometrial receptivity.[12]

Access to early diagnosis and appropriate treatment of endometriosis is crucial, however it remains restricted in numerous contexts, particularly in low- and middle-income countries.[2] Diagnosing endometriosis is not easy. Several studies have shown that an endometriosis diagnosis can be delayed by 7–10 years before it is successfully established.[12] Several factors contribute to the delay in diagnosing endometriosis, such as the early onset of symptoms, pain being considered normal by doctors, and intermittent use of contraceptives leading to hormonal suppression. Additionally, initial misdiagnosis plays a significant role in the delayed diagnosis of endometriosis.[3] A meticulous history of menstruation symptoms and recurrent pelvic pain establishes the foundation for identifying endometriosis. Despite the proposal and testing of various screening strategies and assays, none have been verified to effectively identify or forecast individuals or communities at high risk for the disease.[2] Endometriosis frequently exhibits symptoms that resemble those of other illnesses, leading to a delay in diagnosis.[13] Histologic verification, typically conducted after surgical or laparoscopic visualization, is valuable for confirming diagnoses, especially for prevalent superficial lesions.[14]

No treatments cure the disease.[2] The principle of the treatment is to alleviate the symptoms and prevent further severity. Treatment options for endometriosis are contingent upon the severity of symptoms and the patient's desire for pregnancy. Management of endometriosis-associated pelvic pain involves the suppression of ovulatory menses and estrogen production, the use of cyclooxygenase inhibitors, and surgical excision of pelvic lesions. In vitro fertilization is commonly employed to address infertility issues. Despite the emergence of novel targeted treatments and an improved understanding of endometriosis pathophysiology, straightforward preventive measures like long-term ovulation suppression remain underutilized.[8] Most of the current medical treatments for endometriosis have targeted decreasing estrogen activity. Many endometriosis therapy modalities are established nowadays, including contraceptive steroids, progestogen agents, Gonadotropin-Releasing Hormone (GnRH) agonists such as leuprolide acetate (tapers, divine), danazol, selective progestins such as dienogest (visanne), androgen, and non-steroidal anti-inflammatory agents. This treatment can only be used for a limited period because of its side effects. In addition, a high recurrence rate after treatment becomes a significant problem. Further study of endometriosis treatment strategy is needed to be studied.[7]

The extensive variability in clinical diagnostic timelines may indicate discrepancies in healthcare infrastructure, resources, and skill across various regions and healthcare environments. Despite existing international or national guidelines, healthcare systems and their quality exhibit significant variation among countries.[15,16] This disparity underscores the need for adaptable, cost-effective diagnostic strategies that can be implemented in diverse healthcare settings. In low-resource settings, reliance on symptom-based assessments, clinical history, and basic imaging techniques becomes crucial in the absence of advanced diagnostic tools.[16]

Identifying the challenges in disease diagnosis and the essential components of the treatment strategy. Understanding the disease from the initial presentation is crucial prior to confirmation through surgical intervention and histological analysis. This study seeks to identify specific risk factors and symptoms to facilitate early diagnosis and treatment of endometriosis.

Materials and Methods

Study Design and Settings

This was a case-control study conducted from January 2020 to May 2024 (4.5 years) at Prof. Dr. Margono Soekarjo Provincial General Hospital (RSMS) in Central Java, Indonesia.

Study Population

All patients suffered from Endometriosis since the first coming. The population is divided into which one was true endometriosis confirmed histopathologically and which one was misdiagnosed. The population analyzed the menstrual cycle characteristics and found the association between them then.

Sample Size Estimation

This study utilizes total sampling from 2020 to 2024 at Margono Hospital to compare menstrual cycle characteristics between women with and without endometriosis. This study has calculated the minimum sample size and the minimum effect size using proportions from previous research. The minimum sample size for this study, after applying the formula, is 22. With an additional 15% added to account for potential dropouts, the minimum sample size required is 25. Therefore, this study meets the minimum sample size requirement. Statistical analysis was performed using the IBM SPSS Statistics version 29.0.1.0 (IBM Corp. Released 2023. IBM SPSS Statistics for Window, Version 29.0. Armonk. NY: IBM Corp).

Data Collection

Samples were collected from the interview and registered endometriosis data who come to fertility and endocrinology reproductive polyclinics at the Prof. Dr. Margono Soekarjo Provincial General Hospital. All participants in this research were referral patients clinically diagnosed with endometriosis who were unresponsive to pharmacological and/or hormonal therapy for controlling their pain severity. They agreed to undergo surgical management after receiving an explanation of the therapy algorithm at our institution and signed the informed consent form to participate in the research. The researchers classified the case group as true endometriosis and the control group as non-endometriosis based on histopathological results from laparotomy.

Patients were excluded from the study if they had incomplete medical records or missing data on menstrual history, as well as those diagnosed with other gynecological conditions that could affect menstrual cycles, such as polycystic ovary syndrome (PCOS) or uterine fibroids. Additionally, individuals with a history of pelvic inflammatory disease (PID) or previous pelvic surgery unrelated to endometriosis were not included. Patients currently undergoing hormonal therapy or taking medications that could alter menstrual cycle patterns were also excluded. Furthermore, postmenopausal women or those who had undergone a hysterectomy or oophorectomy prior to the study period were not considered for participation.

The participants were provided explanations about the variables in their native language, based on the operational definitions outlined in this manuscript, during the informed consent process. This included the definition of menstrual

characteristics according to the International Federation of Gynaecology and Obstetrics (FIGO), which was classified using the table that was shown to the participants beforehand. The examiner/clinical healthcare professional was our expert clinical advisor at our institution.

The potential for recall bias in self-reported menstrual characteristics was considered, as participants relied on memory to report cycle patterns, pain severity, and menstrual volume. To minimize this bias, participants were provided with clear definitions, standardized assessment tools such as the Pictorial Blood Assessment Chart (PBAC) for menstrual volume and the Visual Analog Scale (VAS) for pain, and visual references during the informed consent process to enhance the accuracy of their responses.

Menstrual volume was classified using the Pictorial Blood Assessment Chart (PBAC), a standardized tool for assessing menstrual blood loss. To ensure consistency and minimize bias, examples of the PBAC scoring system were demonstrated to participants beforehand, allowing them to accurately categorize their menstrual flow as "light" "normal" or "heavy" based on visual references. This approach enhances the reliability of self-reported menstrual volume data while reducing potential subjectivity in classification.

Onset dysmenorrhea was defined as pain menstrual more than 2 days after the onset of menstrual cycle which occurred <3 years after menarche or >3 years after menarche. Menstrual cycle was classified into 4 categories, frequency, duration, regularity, and bleeding volume. Frequency was classified into 1) absent or amenorrhea, 2) shorten (<24 days), 3) normal (24–38 days), and 4) prolonged (>38 days). Duration was classified into 1) shorten (<4 days), 2) normal (4–8 days), and 3) prolonged (>8 days). Regularity was classified into 1) regular (<7 days), and irregular (>7 days). Volumes were classified into 1) light (<5 cc), 2) normal (80–100cc), and 3) heavy (>100cc).

Dysmenorrhea is defined as menstrual pain associated with underlying pelvic pathology, occurring beyond the first two days of menstruation. The participants were provided explanations about the variables in their native language, following the operational definitions outlined in this manuscript, during the informed consent process. This included the Visual Analogue Scale (VAS), with examples of figures demonstrated to the participants beforehand. The VAS was classified on a scale from 0 to 10, where 0 indicates no pain and 10 represents pain severe enough to prevent daily activities. Contraception was classified based on prior use, type of contraception, and duration of use before the patient was diagnosed with endometriosis. Infertility was defined as the inability of a woman to conceive and give birth to a healthy, living child or the inability of a man to impregnate a partner after 12 months of unprotected, regular sexual intercourse.

Result

Age, parity, and body mass index (BMI) could be potential confounding factors for endometriosis. To address this, we adjusted for these variables in the analysis to minimize bias. Table 1 showed the characteristics of this research. They are age, educational background, parity, dysmenorrhea, dysuria, dyschezia, menstrual cycle, menstrual frequencies, menstrual volume, menstrual interval, infertility, contraception history, and visual analog scale. These factors were carefully considered to ensure that any associations observed were not influenced by confounding variables.

From the variable of age, the reproductive age group (15–49 years) is more prevalent in both groups (45.3% vs 37.5%). Regarding educational background, there is no significant difference between the levels of education and case status ($p = 0.181$). In terms of parity, nulliparity is more common in the endometriosis group (32.8%) compared to the non-endometriosis group (23.4%).

Regarding menstrual pain, there is a statistically significant difference between dysmenorrhea incidence and onset ($p = 0.001$ and $p = 0.045$, respectively) in women with and without endometriosis. Dysuria (42.2%) and dyschezia (42.2%) were more frequently absent in endometriosis cases. In terms of menstrual cycle characteristics, there are no significant differences in menstrual interval, frequency, or regularity between the two groups. However, menstrual volume shows a statistically significant difference ($p = 0.001$) between the endometriosis and non-endometriosis groups.

For infertility and contraception history, there is no significant difference between cases and controls ($p = 0.301$ and $p = 0.570$, respectively). Regarding the visual analog scale (VAS) for pain, a VAS score of 10 (18.8%) is more frequent in women with endometriosis compared to those without endometriosis (9.4%).

Table 1 Basic Characteristics of Endometriosis and Non-Endometriosis Cases

Parameters	Endometriosis (%)	Non-Endometriosis (%)	*p*-Value (Sig. 2-Sided)
Number of cases	34 (54.13)	30 (46.87)	
Age			0.575
Reproductive (15–49 y.o)	29 (45.3)	24 (37.5)	
Non-reproductive (<15 y.o or >49 y.o)	5 (7.8)	6 (9.4)	
Educational Background			0.941
Diploma	2 (3.1)	2 (3.1)	
Undergraduate	2 (3.1)	1 (1.6)	
Senior High School	13 (20.3)	12 (18.8)	
Junior High School	4 (6.3)	2 (3.1)	
Elementary School	8 (12.5)	6 (9.4)	
None	5 (7.8)	7 (10.9)	
Body Mass Index			0.806
Underweight (<18.5kg/m^2)	2 (3.1)	4 (6.3)	
Normoweight (18.5–24.9 kg/m^2)	21 (32.8)	18 (28.1)	
Overweight (25–29.9 kg/m^2)	5 (7.8)	4 (6.3)	
Obese (≥30 kg/m^2)	6 (9.4)	4 (6.3)	
Parity			0.460
Nulliparous	21 (32.8)	15 (23.4)	
Primiparous	4 (6.3)	7 (10.9)	
Multiparous	9 (14.1)	7 (10.9)	
Grand Multiparous	0 (0)	1 (1.6)	
Dysmenorrhea			0.001*
Yes	30 (46.9)	9 (14.1)	
No	4 (6.3)	21 (32.8)	
Onset of Dysmenorrhea			0.045*
<3 years	13 (20.3)	19 (29.7)	
≥ 3 years	21 (32.8)	11 (17.2)	
Dysuria			0.386
Yes	7 (10.9)	9 (14.1)	
No	27 (42.2)	21 (32.8)	
Dyschezia			0.953
Yes	7 (10.9)	6 (9.4)	
No	27 (42.2)	24 (37.5)	
Menstrual Cycle			0.885
Regular	21(32.8)	18 (28.1)	
Irregular	13 (20.3)	12 (18.8)	
Menstrual frequencies			0.413
Shorten (<24 days)	6 (9.4)	3 (4.7)	
Normal (24–37 days)	25 (39.1)	21 (32.8)	
Prolonged (>38 days)	3 (4.7)	6 (9.4)	
Menstrual Volumes			0.001*
Light (<5cc)	0	11	
Normal (5–80 cc)	21 (32.8)	16 (25.0)	
Heavy (>80cc)	13 (20.3)	3 (4.7)	
Menstrual interval			0.134
Prolonged (>8 days)	4 (6.3)	10 (15.6)	
Normal (4.5–8 days)	27 (42.2)	18 (28.1)	
Shorten (<4.5 days)	3 (4.7)	2 (3.1)	
Infertility			0.301
Yes	16 (25.0)	18 (28.1)	
No	18 (28.1)	12 (18.8)	

(*Continued*)

Table 1 (Continued).

Parameters	Endometriosis (%)	Non-Endometriosis (%)	*p*-Value (Sig. 2-Sided)
Contraception History			0.570
Yes	18 (28.1)	18 (28.1)	
No	16 (25.0)	12 (18.8)	
Visual Analog Scale			0.425
Scale 1	1 (1.6)	0	
Scale 2	2 (3.1)	0	
Scale 4	1 (1.6)	3 (4.7)	
Scale 6	3 (4.7)	3 (4.7)	
Scale 7	4 (6.3)	3 (4.7)	
Scale 8	7 (10.9)	12 (18.8)	
Scale 9	4 (6.3)	3 (4.7)	
Scale 10	12 (18,0.8)	6 (9.4)	

Note: *Statistically significant result (p<0.05).

Table 2 Crude OR from Bivariate Analysis, p-value, and Confidence Interval for Dysmenorrhea and Onset of Dysmenorrhea Among Two Study Groups

Parameters	True Endometriosis	Non-endometriosis	OR	p value	CI 95%
Dysmenorrhea					
Yes	30	9	17.5	0.001*	4.754–64.415
No	4	21	0.168		0.065–0.435
Onset of Dysmenorrhea					
≥ 3 years	21	11	2.790	0.045	1.011–7.698
< 3 years	13	19	0.358		0.130–0.989

Note: *Statistically significant result.
Abbreviation: OR, odds ratio.

Table 2 summarizes the association between true endometriosis and occurrence of dysmenorrhea, onset of dysmenorrhea, and menstrual volume seen from the odds ratio using risk analysis. Figure 1 illustrates the percentage distribution of endometriosis and non-endometriosis cases by dysmenorrhea and the onset of dysmenorrhea. From the result,

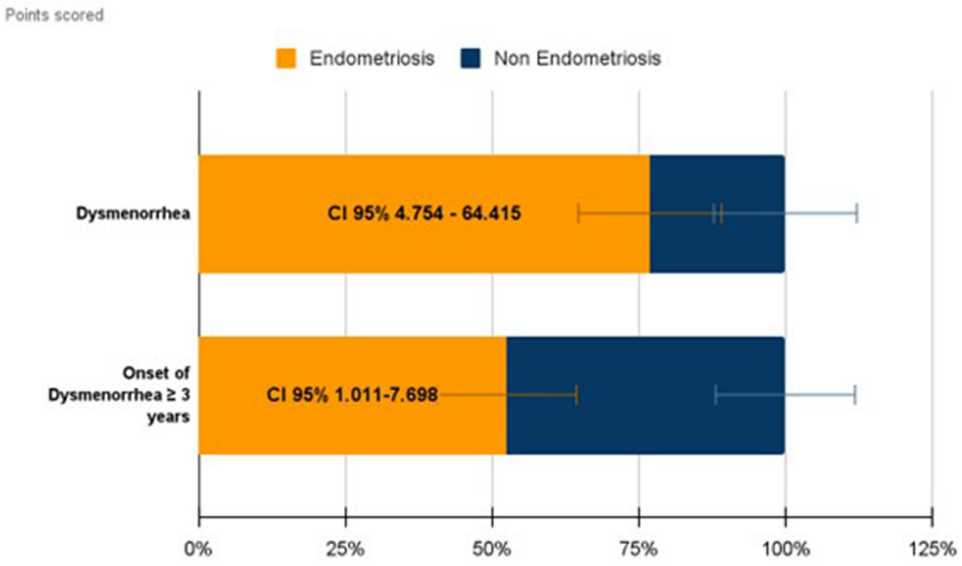

Figure 1 Percentage Distribution of Endometriosis and Non-Endometriosis Cases by Dysmenorrhea and Onset of Dysmenorrhea.

dysmenorrhea has 17.5 times higher odds of occurrence [95% CI = 4.754–64.415] in true endometriosis cases, while the onset of dysmenorrhea being ≥3 years has the 2.79 times odds of occurring [95% CI = 1.011–7.698].

Discussion

At the onset of menstrual pain, our findings indicated a significant difference (p-value 0.045; OR 2.790; CI 95%; 1.011–7.698), with a higher prevalence of dysmenorrhea observed in endometriosis cases (32.8%) compared to non-endometriosis cases (17.2%). Fewer studies have explored modifiable risk factors. It is still an unclear relationship between Endometriosis/EMs and dysmenorrhea in adolescents. A study showed that the onset of dysmenorrhea occurs more than 12 months after menarche has higher risk (OR 5.2) rather than occurs less than 6 months after menarche.[17] A study with a structured self-questionnaire which was developed by a specialist showed the onset of dysmenorrhea occurring >3 years after menarche 3-fold (OR 3.41; CI 95% 2.09–5.64).[18] One of the accepted theories (Sampson's) within studies showed an early age menarche and short cycle length as menstrual characteristic led to the development concept of EMs. Additionally, as hormonal dependent, hormonal changes adaptation may trigger endometrial fragments.[17] As a result, the dysregulated menstrual pathway (angiogenesis, apoptotic regulator, inflammatory, debris clearance and matrix metalloproteinase/MMP) may induce endometrial cells survival and implantation. Although the exact timing of the onset of dysmenorrhea cannot be predicted. As the menstrual cycle matures within 1–4 years, especially dysmenorrhea persisting, it increases the risk of endometriosis if it occurs >3 years as the most common cause of secondary dysmenorrhea. As a conclusion, the onset of dysmenorrhea might become a predictive factor for EM development.[17,18] However, some studies have reported no significant association between menstrual cycle length and endometriosis risk. These inconsistencies may be due to differences in study design, sample size, or diagnostic methods (self-reported vs laparoscopically confirmed cases).[19,20] While our study highlights menstrual characteristics as a potential non-surgical diagnostic tool, other non-invasive methods such as ultrasound and biomarker analysis have also been explored.

Transvaginal ultrasound (TVUS) is widely used for detecting ovarian endometriomas and deep infiltrating endometriosis (DIE). TVUS is the primary imaging modality for diagnosing pelvic endometriosis.[21] It is crucial to acknowledge that there exists considerable variability in the claimed sensitivity and specificity of transvaginal sonography concerning the diagnosis of deep infiltrating endometriosis, regardless of its location.[22]

In contrast, numerous lines of evidence indicate the potential involvement of various biomolecules or biomolecular panels; however, none have demonstrated the requisite test sensitivity and specificity to date.[23] Biomarkers such as CA-125 have been investigated for their diagnostic potential, yet their specificity remains limited,[24] as elevated levels can also be seen in other gynecological conditions.[25] Emerging studies on novel biomarkers, including microRNAs and inflammatory cytokines, suggest promising avenues for non-invasive diagnosis, though these approaches are still under investigation.[26]

Compared to these methods, assessing menstrual characteristics presents a simple, cost-effective, and accessible approach, particularly in low-resource settings where advanced imaging and biomarker testing may not be readily available. The integration of clinical history with non-invasive modalities, including ultrasound and biomarker screening, could facilitate the development of a comprehensive diagnostic pathway for endometriosis, thereby enhancing early detection and patient outcomes.

In our study, we found that both dysuria and dyschezia were not significant and different between levels and cases. As the disease advances, deep infiltrative endometriosis (DIE), characterized by vaginal, intestinal, or bladder infiltration, will lead to the emergence of additional cyclical symptoms over time. Dyschezia may arise from the proximity to the intestine or bowel infiltration, particularly in cases of rectovaginal endometriosis. Cramp like pain prior to bowel movements, irregular stool patterns, and instances of cyclical subileus result from the cyclical swelling of the foci. Additional symptoms, including constipation alternating with diarrhea, paradoxical stools, or pencil-shaped stools, may assist in identifying potential stenosis. Infiltration of the entire intestinal wall by endometriosis may result in cyclical hematochezia.[27] A study centered on predictive models for non-invasive diagnosis of endometriosis based on clinical manifestations. The incidence of dysuria among women with endometriosis is significantly higher, with rates of 32.2% (57 out of 177) compared to 4.3% (4 out of 92) in women without the condition. Furthermore, the incidence of dyschezia

among women with endometriosis is significantly higher, with statistics showing 46.9% (83 out of 177) compared to 15.2% (14 out of 92) in women without the condition. The severity of pain associated with dysuria shows a significant difference (7.5 folds; 1.63 vs 0.22) between the two groups. The severity of pain associated with dyschezia shows a significant difference (3.5 fold) between the two groups.[28]

When examining the characteristics of the menstrual cycle, there are no observed differences or significant variations in menstrual interval, frequency, or regularity. The analysis of menstrual volumes reveals a statistically significant difference (p-value 0.001) between individuals with endometriosis and those without. Heavy menstrual bleeding was identified as the most prevalent symptom and abnormality in patients with endometriosis. One study indicated that menorrhagia was the most prevalent menstrual issue, occurring in 34.6% of cases. Another study indicated that among 200 cases of abnormal uterine bleeding (AUB), 60% exhibited heavy menstrual bleeding.[29]

There are few contrary studies which study between menstrual cycle length with endometriosis. A shortened cycle means increased menstrual frequency and higher risk exposure. Estrogen level increased sharply before the time of ovulation in shortened cycle length.[30] Additionally, estrogen has linear effects of insulin growth factor (IGF-1) or vascular endothelial growth factor (VEGF) on ectopic endometrial tissue.[31] A case–control study showed that endometriosis women have a menstrual cycle length <4 weeks rather than >6 weeks without endometriosis women.[32] A meta-analysis showed consistency of menstrual cycle length shorter than or equal to 27 days (OR 1.22; 95% CI 1.05–1.43) or longer than equal to 29 days (OR 0.68; 95% CI 0.48–0.96) has different risk.[33]

A pilot study showed that endometriosis women have more heavy menstrual flow rather than without endometriosis frequently, but it did not reach statistical significance. The Pictorial Blood Loss Assessment (PBAC) as a score system has the highest sensitivity (91%) and specificity (81%) with 130 cc as the cut-off value. The prevalence of menorrhagia is higher in endometriosis women rather than without endometriosis (63% vs 61%). But there is still an unclear explanation.[34] Sampson's Theory believes that the steroid length exposure as hormonal dependent such as shortened cycle length, long menstrual duration, and low parity are possible risk factors. A case-control study showed that both heavy menstrual flow and length menstrual duration were not statistically significant. There is only length menstrual cycle shown 25–29 days has highest risk (OR 3.8; 95% CI 0.8–18.8) seen on menstrual characteristic.[35]

In our study, we found that the menstrual pain, there is significance for dysmenorrhea (*p-value* 0.001; OR 17.5; CI 95% 4.754–64.415) with incidences higher in endometriosis cases (46.9%) rather than non-endometriosis (14.1%). However, the wide confidence interval suggests potential variability in the data, which may be attributed to a smaller sample size or heterogeneity within the study population. This variability underscores the need for further research with larger sample sizes to improve precision in estimating the true effect size.

Dysmenorrhea is one of the primary clinical manifestations of endometriosis.[36] Few studies focusing on prior dysmenorrhea on adolescent and young adults which have long-term consequences that have a negative effect. It could be one of the potential predictive indicators for detecting in the early stage.[36,37] A study of logistic regression showed that dysmenorrhea frequency and onset of dysmenorrhea are statistically significant. Individuals with high-frequency dysmenorrhea are more likely to have endometriosis (OR 3.1; 95% CI 1.9–5.2), while those with persistent dysmenorrhea exhibit an even greater likelihood of having endometriosis (OR 10.1; 95% CI 5.1–19.7) compared to those without dysmenorrhea. The study identified an independent risk factor for the predictive efficacy of EMs.[17] Relevant elevated levels of proinflammatory factors such as IL-6, IL-8, tumor necrosis factor (TNF-alpha), and prostaglandin (PGE2). Inflammation and cellular damage are responsible for the pain, which resolves as the reaction diminishes. The cyclic release of pain and inflammatory mediators activates visceral and peritoneal nerve fibers, resulting in heightened pain sensitivity.[27] The pain on EMs was associated with multiple factors such as EMs tissues and cytokines which led to developing mechanisms. In addition, an ectopic endometrial led to EMs sporadic. The two may be a causative and effect of each other.[17]

In our study, we found that the visual analog scale, on pain scale 10 (18.8%) is higher on endometriosis women rather than non-endometriosis (9.4%). A systematic review proved that VAS and Numeric Rating Scale (NRS) type scales have been compared for endometriosis-related pain.[38] It was proven that VAS has a strong correlation between poor quality of life impact and pain scale severity. A study showed that endometriosis women had a high score (>7) as prevalent VAS cut-off point.[39] The study strengthened the fact that dysmenorrhea was more frequent (VAS 7; mean score 5.76)

adolescent complaints rather than dyschezia (1.19), dysuria (0.19), chronic pelvic pain/CPP (2.55), and dyspareunia (2.87). And, the linear regression showed that age could affect the pain associated with dyschezia (R: 0.03), dyspareunia (R: 0.02), and dysmenorrhea (R:0.01).[40] A study showed neuropathic pain-related endometriosis was spreading lower back, lower abdomen, thigh/lower extremities and hips compared to non-endometriosis women.[28]

In our study, we found that in the infertility and contraception history, there are no difference and significance between levels and cases (0.301 v 0.570). The ectopic endometrial fragments were associated sex hormone mediated inflammation. There were 2 contrary, prior oral contraceptives (OCPs) as a protector and prior OCPs as a mediator. First, the prior exogenous hormone exposure reduced endometrial fragments which were implanted in the peritoneal by retrograde menstruation. Second, the prior exogenous hormone exposure increased the possibility of ectopic endometrial development.[41] Endometriosis women began to use the hormonal contraceptive (HC) at higher risk from 12 to 14 years old (aHR 2.53; 95% CI 2.21–2.90) rather than older than 17 years old. Additionally, they had tried 3 types of HC that had higher risk (aHR 2.31; 95% CI 1.71–3.13) rather than 1 type.[42]

As for duration usage, a study showed that using HC for more than 1 year decreased the risk of endometriosis (aHR 0.53; 95% CI 0.48–0.59). HC has varian mechanisms. Hormonal treatment was believed to reduce the endometrioma diameter. For example, progestin has an effect to prevent angiogenesis, endometrial cell propagation directly and modulate the immune system indirectly. It also acts as an anti-inflammatory and decreased MMP which reduced endometrial cell invasiveness. On the central mechanism, it suppressed gonadotropin secretion which made it a hypoestrogenic state.[42,43] Inversely, another study showed that OCP usage more than 5 years has higher risk (OR 2.42; 95% CI 1.76–3.33) rather than less than 5 years (OR 2.13; 95% CI 1.6–2.8) on endometriosis development. Unfortunately, this study did not mention any kind of contraception observed. A comparative study for looking at menstrual pain relief after taking progestin or combination oral contraceptive/COC for 3 years showed pain level improvement in both groups.[43]

Mechanical disruption such as pelvic adhesions which occurred in endometriosis contributes to oocyte release impairment, pick up and alter sperm motility, causing disordered myometrial contractions and impairing fertilization and embryo transport.[44] The elevated presence of inflammatory cells in the peritoneal fluid and endometriomas led to changes in the quality of ovulation, oocyte production, and detrimental effects on the embryo. Furthermore, there is a reduction in sperm quantity, which is suggested to be a consequence of the inflammatory response observed in peritoneal fluid, along with an increase in activated macrophages. The disruption of the immune system caused by the T-cell regulator was inhibited by inflammatory mediators, including cytokines, chemokines, and prostaglandin. The disruption of the luteal phase is attributed to dysregulation of progesterone receptors and their impact on progesterone target genes, resulting in reduced endometrial receptivity. Endometriosis, being an estrogen-dependent condition, is influenced by an increase in aromatase, the enzyme responsible for converting androstenedione and testosterone into estrone and estradiol. This elevation in aromatase activity results in heightened estrogen production within the endometrium, which adversely affects endometrial development and receptivity, ultimately leading to implantation failure.[44,45] A study showed prevalence of endometriosis higher significantly in women with primary infertile (56%; 82/147) than secondary infertile (30%; 22/74).[46] A systematic review indicated that the prevalence of endometriosis is approximately 44% (1707 samples) among cases of unexplained infertility, as confirmed by laparoscopy.[47]

Effective management of endometriosis in low-resource settings necessitates a balanced integration of medical and surgical interventions to enhance the quality of life for patients. Hormonal treatments, including combined oral contraceptives, progestins, and gonadotropin-releasing hormone (GnRH) agonists, are frequently employed to inhibit disease progression and mitigate symptoms through the reduction of estrogen levels.[48] Nonsteroidal anti-inflammatory drugs (NSAIDs) are essential in alleviating pain related to dysmenorrhea, providing a readily available and economical solution for symptom management. In instances where medical therapy proves ineffective or is contraindicated, surgical intervention may be required.[49]

Laparoscopic surgery is considered the standard approach for diagnosing and treating endometriosis; however, its availability is frequently restricted in resource-limited settings.[50] In these contexts, the optimization of conservative surgical techniques, including ablation or excision of lesions, may yield long-term symptom relief and enhance fertility outcomes.[49] Enhancing healthcare infrastructure, expanding physician training, and incorporating cost-effective treatment

strategies are crucial for improving the management of endometriosis in these contexts. A multidisciplinary approach that integrates medical and surgical options, adapted to available resources, can markedly improve the quality of life for affected individuals.

Conclusion

This study highlights the significant association between specific characteristics, such as the onset and duration of dysmenorrhea and the occurrence of endometriosis. The findings suggest that dysmenorrhea, particularly when it begins more than three years after menarche, is a strong predictor of endometriosis. Given the challenges in early diagnosis, the study emphasizes the potential for using these initial signs and symptoms to develop non-surgical diagnostic approaches. Early identification could lead to more effective management and improved outcomes for women suffering from endometriosis.

Data Sharing Statement

Datasets used in this article are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Prof. Dr. Margono General Hospital with number of 420/10313. Informed consent was obtained from all individual participants included in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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